An *Ab Initio* Interpretation in Gas Phase and Aqueous Solution of the Generalized Anomeric Effect in R—O—CR_2—NR_2 (R = H, CH_3)

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ABSTRACT: The conformational stability of aminomethanol and its methylated derivatives has been investigated by means of *ab initio* methods in the gas phase and aqueous solution. Among the computational levels employed, HF/6-31G**//HF/6-31G** calculations correctly describe the conformational features of this series of compounds, and agree well with the results obtained using larger basis sets and including ZPE or electron correlation corrections. Calculated energies and geometries follow the known trends associated to the generalized anomeric effect. Thus, the most stable conformers exhibit preferences for the *trans* orientations of the Lp—N—C—O and Lp—O—C—N moieties. However, reverse anomeric effects are observed when a methyl group is bonded to the oxygen, because the Lp—O—C—N unit prefers a *gauche* orientation (that is, *trans* Me—O—C—N). The natural bond orbital (NBO) method was employed to explain the cited conformational preferences. According to the NBO results, *trans* arrangements are preferred because the stabilization due to charge delocalization is more important than electrostatic and steric contributions. This explanation agrees with the conclusions obtained by other independent procedures based on energy decomposition schemes. The NBO method was also used to explain the origin of the rotational barriers around the C—O and C—N bonds in terms of the balance between unfavorable hyperconjugation and electrostatic and steric effects. Changes in conformational stability caused by methylations in different molecular positions were also explained by the influence of the methyl groups on lone-pair delocalization and on steric effects. Finally, the effect of solvation was studied by means of the *ab initio* PCM method,

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and the significant changes on relative energies found were analyzed. © 2000 John Wiley & Sons, Inc. J Comput Chem 21: 462–477, 2000

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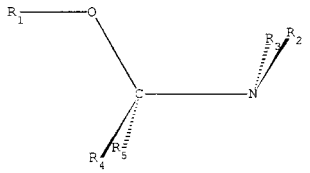
Introduction

According to the so-called generalized anomeric effect,[1] the aliphatic compounds R—X—A—Y prefer the *gauche* conformation to the *anti*, in which A is an element of medium electronegativity (e.g., C), Y is more electronegative than A (e.g., O or N), X is an element with lone pairs, and R is C or H. The electrostatic model of dipole interaction, which was applied for the first time in 1955 by Edward[2] to explain the destabilization of the equatorial conformations in sugars, is based on the notion that the repulsions between the dipole of the X lone pairs and the A–Y dipole destabilize the *anti* conformation. A different explanation is based on the model of charge delocalization. This model was originally applied to explain the geometric distortions of the 2,5-dichloro-l,4-dioxanes,[3a] and it was stated that the stability of the *gauche* forms is due to the delocalization of one X lone pair in the *anti*-bonding orbital A–Y.[3b] From the available experimental and theoretical evidence it is generally accepted that, depending on the molecular systems, both the dipole repulsions and charge delocalization factors can contribute to the anomeric effect.[1a, 4]

Numerous studies have shown that *ab initio* MO calculations adequately reproduce the energetic stabilities as well as the geometric tendencies in bond lengths and bond angles associated with the anomeric effect, both in linear and cyclic compounds. However, despite the efforts made, because of the structural complexity of the majority of the anomeric molecules, there is still no general explanation for the conformational preferences of systems containing the O—C—O, N—C—N, and O—C—N units.[1a, 5] In particular, different interpretations of the origin of the anomeric effect have been reported for R—O—CR_2—NR_2 (R = H, CH_3) compounds. Thus, Kaliannan et al.[6] have carried out HF/STO-3G and HF/4-31G calculations and compared the potential energy surface of aminomethanol and methanediol. The favored conformations are discussed in terms of interactions between polar bonds and atomic dipoles, by means of a three-term Fourier energy decomposition representing dipolar effects, electron delocalizations, and steric factors. El-Issa and Budeir[7a] studied the HF/3-21G energies of aminomethanol using a rigid rotor model and a Fourier expansion of the potential energy in dipolar, steric, and orthogonal factors. They found that the hydrogen of the OH group has an almost free rotation around the C—O bond, and verified their conclusions with completely relaxed 6-31G* calculations, also carried out on methanediol.[7b] Grein and Deslongchamps[8] studied the anomeric effects in aminomethanol and methanediol, among other compounds, using HF/6-31G** calculations and a simple model of Fourier energy decomposition in terms of steric, electrostatic (lone pair–lone pair, lone pair–hydrogen), and electronic contributions. Smits et al.[1c] used a model based in charge transfer, interference, and quasi-classical interactions, which allows the analysis of HF functions built approximately with nonortogonalized localized molecular orbitals. They concluded that the anomeric stabilization in aminomethanol is fundamentally due to interference interactions. According to Chang and Su,[9] for the anomeric compounds methanediol, aminomethanol, and methanediamine, there is an unambiguous conformational energy decomposition based on through-direct-bond decoupled-rotor potentials and through-space electrostatic potentials. The first potentials are considered as three conventional Fourier terms, and the second ones are general forms of the dipole–dipole, dipole–quadrupole, and quadrupole–quadrupole interactions. These authors conclude that the decoupled potentials are due to charge delocalizations of the type n_X–σ^*_{CY} (X, Y = O, N), which are the main responsible of the relative energy ordering. The delocalization effect is attenuated by the opposing effect caused by electrostatic interactions. They also concluded that the traditional explanation for the anomeric effect based on electric dipole–dipole interaction should be questioned. Finally, in several studies, the NBO analysis of Hartree–Fock wave functions[10] using ortogonalized atomic orbitals has supported the model of charge delocalization.[11]

According to the above, the aim of this study is to contribute to the interpretation of the gener-



Compound	1	2	3	4	5	6	7	8	9	10
R_1	H	Me	-	-	-	Me	Me	-	-	Me
R_2	H	-	-	-	-	Me	Me	Me	-	-
R_3	H	-	-	-	Me	-	Me	Me	Me	-
R_4	H	-	-	Me	-	-	-	-	Me	-
R_5	H	-	Me	Me	-	-	-	-	-	Me

SCHEME 1. Atom numbering and notation employed for the compound studied.

alized anomeric effect, and provide a satisfactory explanation for the conformational energies, rotational barriers, and geometric tendencies in linear compounds with the R—O—C—N unit. To this end, *ab initio* MO calculations and NBO analyses have been carried out on the following substances (see Scheme 1): aminomethanol (**1**), 1-methoxy-methanamine (**2**), 1-aminoethanol (**3**), 2-amino-2-propanol (**4**), methylaminomethanol (**5**), 1-methoxy-*N*-methylmethanamine (**6**), 1-methoxy-*N*,*N*-dimethylmethanamine (**7**), dimethylaminomethanol (**8**), 1-methylaminoethanol (**9**), 1-methoxy-1-aminoethanol (**10**). Although hardly any experimental structural information of these substances has been published, this selection allows us to analyze in detail the parent compound of the series (aminomethanol), and the repercussions of the different mono- and bimethylations of the N—C—O unit. We have already published partial theoretical results about these compounds at the HF/4-21G[12] and HF/6-31G*[13] levels. However, as unpolarized basis sets overestimate anomeric effects,[11] here we complete previous studies including diffuse and polarization functions in the basis set. Employing the NBO analysis of the HF wave functions, the hyperconjugative energetic contribution can be separated from that due to steric and electrostatic effects. It should be also noted that the anomeric axial preferences of compounds with the endocyclic O—C—N unit were properly explained with the NBO method.[11d] Finally, as a reduction of the anomeric effect on polar solvents has been observed theoretically[14a] and experimentally,[14b, 14c] we have also included here an estimate of the influence of water on the conformational stability by means of an *ab initio* procedure for the study of solvent effects.

Method

All the compounds cited previously were optimized at the HF/6-31G** level, taking all the staggered conformations for each compound as starting points. Because of the presence of lone pairs, single-point calculations were then performed using the 6-31++G** basis set to establish the effect of diffuse functions. To take the effect of the electron correlation into account, MP2/6-31G** and MP2/6-31++G** single-point calculations were also included. Finally, MP2/6-31G** optimizations were also performed to analyze the influence of electron correlation on the geometries. The HF/6-31G** vibrational frequencies and the zero-point energy (ZPE) of each conformation were evaluated. The Gaussian 94 program[15] was used in this study.

The possible conformers for the compounds studied are shown in Figure 1. They will be noted by the number of each compound followed by two letters representing the approximate value ($G = 60°$, $G' = -60°$, $T = 180°$) of the principal dihedral angles, X—O—C—N (X = C or H) and Lp—N—C—O, in this order. To analyze the origin of the rotational barriers, we also performed additional HF/6-31G** optimizations of a series of structures with a fixed value of one dihedral angle, while varying the other in a range of 360° in intervals of 20°. From now on, this kind of calculation will be indicated as

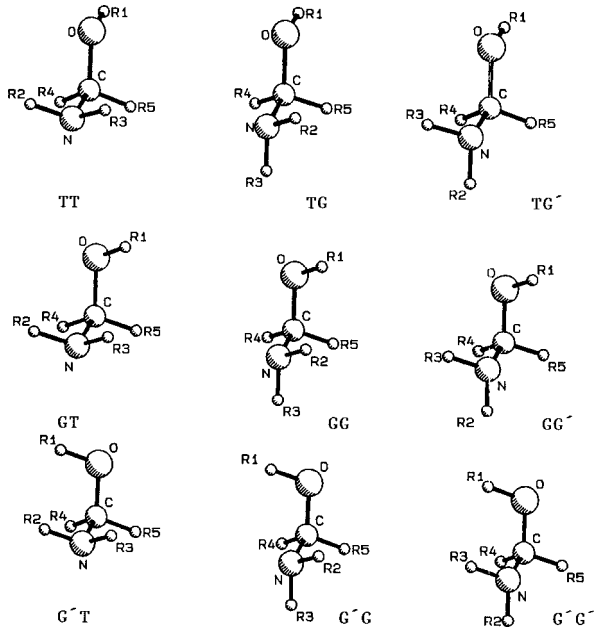


FIGURE 1. Representation of the different conformations of the compounds defined in Scheme 1.

(G; Lp—N—C—O), which means the geometrical optimization of structures with X—O—C—N fixed at 60°, while the full range (360°) of Lp—N—C—O angles is covered.

The NBO calculations were carried out employing the HF/6-31G** wave functions corresponding to the HF/6-31G** and MP2/6-31G** geometries. We observed that the NBO results for HF and MP2 geometries are similar; therefore, the results on the MP2 geometries are not included here. According to the NBO method,[10, 11] E_{tot} represents the total SCF relative energy, and E_{Lew} is the energy associated with the localized part of the HF wave function (corresponding essentially to a Lewis structure, although its interpretation is not direct). The Lewis energy is obtained by zeroing all the orbital interactions, that is, deleting the off-diagonal elements of the Fock matrix. Finally, the delocalization energy, which corresponds to all the possible interactions between orbitals, is calculated as $E_{del} = E_{tot} - E_{Lew}$.

The influence of water was evaluated using the polarized continuum model (PCM), which has been applied successfully to other anomeric systems.[14c] The 6-31G** basis set was used along with the gas phase optimized geometries at the same level. A detailed description of the PCM method is beyond the scope of this study,[16] but it should be recalled that the free solvation energy of the solute M, ΔG_{sol}, due to the dipole–solvent interactions, can be broken down into the following components:

$$\Delta G_{sol} = \Delta G_{el} + \Delta G_{noel} = \Delta G_{el} + \Delta G_{cav} + \Delta G_{dis\text{-}rep}$$

in which ΔG_{el} represents the electrostatic interaction between the solute and the solvent, and the nonelectrostatic term, ΔG_{noel}, is formed by the cavitation energy, ΔG_{cav}, calculated for a cavity formed by van der Waals spheres, and a repulsive–dispersive contribution, $\Delta G_{dis\text{-}rep}$, calculated by atom–atom coefficients.

Results

GENERAL CONSIDERATIONS

The relative energies for the conformers of each compound at several computational levels and the energetic contributions in the NBO model are detailed in Tables I and II. The HF/6-31G** dipolar moments are also included in Table II, because it has been suggested that in the gas phase there is a relationship between higher stability and smaller dipolar moments, although there are proven cases that do not follow this rule.[5c] To complete the study and make it comparative, previously published theoretical information obtained with different basis sets and complete geometrical optimization has been also included. The analysis of the relative energies in Table I allow us to establish a series of general considerations about the influence of the basis set, the electron correlation, and the ZPE on the stability of the conformers. Thus, the 4-21G basis set does not seem acceptable, because the predicted stability orderings are frequently in contradiction with those obtained with larger basis sets. It also overestimates the relative energy of the less stable conformers, and it is frequently unable to localize some local minima. For an extensive set of anomeric compounds of the type X—CH_2—O—CH_3, an analogous conclusion was achieved because 6-31G*//4-21G calculations were stated as the minimum level nec-

TABLE I.
Relative Energies (kcal/mol) at Various Computational Levels for the Stable Conformers of the Compounds of Scheme 1.

Aminomethanol	**1**TT	**1**TG	**1**TG′	**1**GT	**1**GG	**1**GG′	**1**G′T	**1**G′G	**1**G′G′
HF/3-21G//HF/3-21G[18b]	1.40	7.89		0.00		1.25			
HF/4-21G//HF/4-21G[19]	1.12			0.00		1.26			
HF/6-31G*//HF/6-31G*[13]	0.14			0.00		0.52			
HF/6-31G**//HF/6-31G**	0.17	4.99	**1**TG	0.00	*ts*	0.60	**1**GT	**1**GG′	**1**GG
HF/6-31G**//HF/6-31G** + ZPE	0.10	4.59		0.00		0.62			
HF/6-31++G**//HF/6-31G**	0.06	4.51		0.00		0.39			
MP2/6-31G**//HF/6-31G**	0.45	5.67		0.00		0.96			
MP2/6-31++G**//HF/6-31G**	0.39	5.17		0.00		0.71			
MP2/6-31G**//MP2/6-31G**	0.53	5.67		0.00		0.99			
HF/6-311+G(2d,p)//MP2/6-31G(2d,p)[9]	-0.14	4.03		0.00		0.32			
MP2/6-311+G(2d,p)//MP2/6-31G(2d,p)[9]	0.22	4.51		0.00		0.66			

TABLE I.
(Continued)

1-Methoxy-methanamine	**2**TT	**2**TG	**2**TG′	**2**GT	**2**GG	**2**GG′	**2**G′T	**2**G′G	**2**G′G′
HF/3-21G//HF/3-21G[18b]	0.95			0.00					
HF/4-21G//HF/4-21G[12a]	0.70	7.26		0.00		*nf*			
HF/4-21G(*N)//HF/4-21G(N*)[17]	0.11	6.18		0.00		2.31			
HF/6-31G*//HF/4-21G(N*)[17]	0.00	5.20		0.79		2.47			
HF/6-31G*//HF/6-31G*[13]	0.00			0.83					
HF/6-31G**//HF/6-31G**	0.00	4.88	**2**TG	0.82	*ts*	2.42	**2**GT	**2**GG′	**2**GG
HF/6-31G**//HF/6-31G** + ZPE	0.00	4.53		0.89		2.35			
HF/6-31++G**//HF/6-31G**	0.00	4.48		0.96		2.31			
MP2/6-31G**//HF/6-31G**	0.00	5.32		0.34		2.36			
MP2/6-31++G**//HF/6-31G**	0.00	4.87		0.44		2.11			
MP2/6-31G**//MP2/6-31G**	0.00	5.26		0.25		2.31			
1-Aminoethanol	**3**TT	**3**TG	**3**TG′	**3**GT	**3**GG	**3**GG′	**3**G′T	**3**G′G	**3**G′G′
HF/3-21G//HF/3-21G[18b]	1.14			0.00		0.85	0.12	0.90	
HF/4-21G//HF/4-21G[12b]	0.90	*nf*	6.38	0.00	7.30	0.82	0.15	0.77	*nf*
HF/6-31G**//HF/6-31G**	0.03	4.81	3.94	0.11	*ts*	0.20	0.00	0.13	*nf*
HF/6-31G**//HF/6-31G** + ZPE	0.03	4.47	3.69	0.11		0.27	0.00	0.20	
HF/6-31++G**//HF/6-31G**	0.07	4.70	3.68	0.25		0.16	0.00	0.07	
MP2/6-31G**//HF/6-31G**	0.08	4.97	4.25	0.00		0.30	0.01	0.22	
MP2/6-31++G**//HF/6-31G**	0.22	5.09	3.98	0.23		0.28	0.00	0.31	
MP2/6-31G**//MP2/6-31G**	0.17	4.99	4.31	0.00		0.37	0.04	0.27	
2-Amino-2-propanol	**4**TT	**4**TG	**4**TG′	**4**GT	**4**GG	**4**GG′	**4**G′T	**4**G′G	**4**G′G′
HF/3-21G//HF/3-21G[18b]	0.88			0.00		0.63			
HF/4-21G//HF/4-21G[12c]	0.63	*nf*		0.00		0.46			
HF/6-31G**//HF/6-31G**	0.00	4.20	**4**TG	0.06	*ts*	0.05	**4**GT	**4**GG′	**4**GG
HF/6-31G**//HF/6-31G** + ZPE	0.00	3.90		0.03		0.09			
HF/6-31++G**//HF/6-31G**	0.07	4.10		0.08		0.00			
MP2/6-31G**//HF/6-31G**	0.00	4.31		0.04		0.09			
MP2/6-31++G**//HF/6-31G**	0.13	4.43		0.00		0.18			
MP2/6-31G**//MP2/6-31G**	0.04	4.30		0.00		0.11			
Methylaminomethanol	**5**TT	**5**TG	**5**TG′	**5**GT	**5**GG	**5**GG′	**5**G′T	**5**G′G	**5**G′G′
HF/3-21G//HF/3-21G[18b]	1.52		7.22	0.00		1.93	0.46	0.80	
HF/4-21G//HF/4-21G[12a]	1.29	7.02	6.62	0.37	*nf*	0.73	0.00	1.65	*nf*
HF/6-31G**//HF/6-31G**	0.44	4.23	4.16	0.00	4.34	0.09	0.03	1.00	4.04
HF/6-31G**//HF/6-31G** + ZPE	0.28	3.81	3.79	0.00	3.96	0.12	0.00	0.26	3.69
HF/6-31++G**//HF/6-31G**	0.22	3.84	3.74	0.00	4.13	0.04	0.10	0.08	3.81
MP2/6-31G**//HF/6-31G**	0.81	5.20	4.61	0.00	5.08	0.33	0.04	0.86	4.37
MP2/6-31++G**//HF/6-31G**	0.52	4.87	4.03	0.00	4.95	0.20	0.04	0.69	4.13
MP2/6-31G**//MP2/6-31G**	0.88	5.23	4.63	0.00	5.13	0.36	0.04	0.91	4.42

essary to predict energy differences in agreement with experimental information.[17] Even more, for **2** and other compounds containing the NH_2 group, it had been shown that polarization functions are needed, at least on the N, to eliminate the excessive tendency of the NH_2 group to adopt planar conformations during the geometric optimization.[17] Although there are not available data for all the compounds, the relative energies obtained with the 3-21G basis set behave in a similar way to that

TABLE I.
(Continued)

1-Methoxy-*N*-methylmethanamine	**6**TT	**6**TG	**6**TG′	**6**GT	**6**GG	**6**GG′	**6**G′T	**6**G′G	**6**G′G′
HF/4-21G//HF/4-21G[12b]	0.73	6.16	6.52	0.00		2.48	2.09	1.53	*nf*
HF/6-31G*//HF/6-31G**	0.00	3.90	3.96	0.61	*ts*	1.78	*nf*	1.52	5.05
HF/6-31G**//HF/6-31G** + ZPE	0.00	3.66	3.68	0.69		1.78		1.50	4.93
HF/6-31++G**//HF/6-31G**	0.00	3.63	3.69	0.77		1.84		1.57	4.83
MP2/6-31G**//HF/6-31G**	0.00	4.11	4.74	0.00		1.93		1.18	5.09
MP2/6-31++G**//HF/6-31G**	0.00	3.76	4.60	0.00		2.01		1.08	4.76
MP2/6-31G**//MP2/6-31G**	0.15	4.20	4.84	0.00		2.03		1.27	*nf*
1-Methoxy-*N*,*N*-dimethylmethanamine	**7**TT	**7**TG	**7**TG′	**7**GT	**7**GG	**7**GG′	**7**G′T	**7**G′G	**7**G′G′
HF/3-21G//HF/3-21G[18b]	0.00	4.56							
HF/4-21G//HF/4-21G[12a]	0.00	4.86		*nf*		0.50			
HF/6-31G**//HF/6-31G**	0.00	3.21	**7**TG	*nf*	*ts*	0.85	**7**GT	**7**GG′	**7**GG
HF/6-31G**//HF/6-31G** + ZPE	0.00	3.01				0.87			
HF/6-31++G**//HF/6-31G**	0.00	2.96				0.98			
MP2/6-31G**//HF/6-31G**	0.00	3.42				0.36			
MP2/6-31++G**//HF/6-31G**	0.00	3.11				0.38			
MP2/6-31G**//MP2/6-31G**	0.00	3.36				0.30			
Dimethylaminomethanol	**8**TT	**8**TG	**8**TG′	**8**GT	**8**GG	**8**GG′	**8**G′T	**8**G′G	**8**G′G′
HF/4-21G//HF/4-21G[12c]	1.23	5.95		0.00	5.67	0.40			
HF/6-31G*//HF/6-31G*[13]	0.96			0.18		0.00			
HF/6-31G**//HF/6-31G**	0.98	3.88	**8**TG	0.25	3.68	0.00	**8**GT	**8**GG′	**8**GG
HF/6-31G**//HF/6-31G** + ZPE	0.74	3.45		0.21	3.41	0.00			
HF/6-31++G**//HF/6-31G**	0.71	3.47		0.28	3.59	0.00			
MP2/6-31G**//HF/6-31G**	1.24	4.13		0.07	3.64	0.00			
MP2/6-31++G**//HF/6-31G**	0.89	3.61		0.10	3.64	0.00			
MP2/6-31G**//MP2/6-31G**	1.27	*nf*		0.03	3.63	0.00			
1-Methylaminoethanol	**9**TT	**9**TG	**9**TG′	**9**GT	**9**GG	**9**GG′	**9**G′T	**9**G′G	**9**G′G′
HF/4-21G//HF/4-21G[12c]	1.11	6.03	7.31	0.49	*nf*	1.51	0.00	2.53	*nf*
HF/6-31G**//HF/6-31G**	0.29	4.21	5.91	0.00	4.57	1.36	0.16	1.21	6.05
HF/6-31G**//HF/6-31G** + ZPE	0.21	3.96	5.71	0.00	4.32	1.57	0.14	1.42	5.85
HF/6-31++G**//HF/6-31G**	0.24	3.93	5.80	0.00	4.28	1.40	0.39	1.16	6.14
MP2/6-31G**//HF/6-31G**	0.45	4.45	5.90	0.00	4.87	1.19	0.08	1.10	6.00
MP2/6-31++G**//HF/6-31G**	0.44	4.26	5.82	0.00	4.60	1.20	0.37	1.04	6.32
MP2/6-31G**//MP2/6-31G**	0.54	4.48	5.89	0.00	4.89	1.20	0.07	1.14	6.02
1-Methoxy-1-aminoethanol	**10**TT	**10**TG	**10**TG′	**10**GT	**10**GG	**10**GG′	**10**G′T	**10**G′G	**10**G′G′
HF/6-31G**//HF/6-31G**	0.58	5.38	4.43	2.23	*ts*	3.26	0.00	1.25	*ts*
HF/6-31G**//HF/6-31G** + ZPE	0.59	4.96	4.22	2.37		3.31	0.00	1.13	
HF/6-31++G**//HF/6-31G**	0.52	5.01	3.96	2.30		3.11	0.00	1.14	
MP2/6-31G**//HF/6-31G**	0.59	5.92	4.72	1.94		3.27	0.00	1.42	
MP2/6-31++G**//HF/6-31G**	0.54	5.66	4.15	1.93		2.85	0.00	1.43	
MP2/6-31G**//MP2/6-31G**	0.65	5.85	4.74	1.90		3.29	0.00	1.47	

ts: Structure characterized as transition state by vibrational analysis at this computational level.
nf: Structure not characterized as minimum or transition state at any computational level.

TABLE II.

HF/6-31G Relative Energies (E_{tot}), Lewis Energies (E_{Lew}), and Contributions from Hyperconjugation (E_{del}) for the Stable Conformers of the Compounds of Scheme 1.**

	E_{tot}	E_{Lew}	E_{del}	μ		E_{tot}	E_{Lew}	E_{del}	μ
1TT	0.17	−3.95	4.12	1.30	**2**TT	0.00	0.00	0.00	1.12
1TG	4.99	−3.32	8.31	2.91	**2**TG	4.88	1.16	3.71	2.49
1GT	0.00	0.00	0.00	1.82	**2**GT	0.82	5.45	−4.63	1.63
1GG′	0.60	−5.03	5.63	1.96	**2**GG′	2.42	−0.79	3.21	1.62
3TT	0.03	−2.49	2.52	1.30	**4**TT	0.00	0.00	0.00	1.27
3TG	4.81	−1.11	5.92	2.79	**4**TG	4.20	0.52	3.68	2.58
3TG′	3.94	−3.20	7.14	2.67	**4**GT	0.06	2.72	−2.66	1.59
3GT	0.11	2.09	−1.98	1.71	**4**GG′	0.05	−1.83	1.88	1.70
3GG′	0.20	−4.09	4.29	1.79					
3G′T	0.00	0.00	0.00	1.69					
3G′G	0.13	−3.67	3.80	1.83					
5TT	0.44	−4.28	4.72	1.17	**6**TT	0.00	0.00	0.00	0.95
5TG	4.23	−3.45	7.68	2.43	**6**TG	3.90	2.00	1.90	2.19
5TG′	4.16	−2.68	6.84	2.62	**6**TG′	3.96	1.02	2.94	2.03
5GT	0.00	0.00	0.00	1.55	**6**GT	0.61	5.83	−5.22	1.60
5GG	4.33	−2.28	6.62	2.76	**6**GG′	1.78	−1.96	3.74	1.23
5GG′	0.09	−5.14	5.23	1.93	**6**G′G	1.52	−0.28	1.80	1.59
5G′T	0.03	0.22	−0.19	1.83	**6**G′G′	5.05	1.74	3.31	2.33
5G′G	0.25	−6.04	6.28	1.66					
5G′G′	4.04	−0.69	4.72	2.69					
7TT	0.00	0.00	0.00	0.95	**8**TT	0.98	1.56	−0.58	1.23
7TG	3.21	1.37	1.84	1.84	**8**TG	3.88	2.79	1.09	2.27
7GG′	0.85	−1.65	2.50	1.28	**8**GT	0.25	5.92	−5.67	1.59
					8GG	3.68	4.40	−0.71	2.39
					8GG′	0.00	0.00	0.00	1.65
9TT	0.29	−3.33	3.63	1.18	**10**TT	0.58	−3.66	4.25	1.17
9TG	4.21	−4.42	8.63	2.07	**10**TG	5.38	−4.75	10.13	1.87
9TG′	5.91	0.90	5.02	2.51	**10**TG′	4.43	−3.70	8.13	2.48
9GT	0.00	0.00	0.00	1.45	**10**GT	2.23	3.63	−1.39	1.60
9GG	4.57	−4.33	8.90	2.56	**10**GG′	3.26	−4.03	7.29	1.47
9GG′	1.36	−2.62	3.99	1.76	**10**G′T	0.00	0.00	0.00	1.50
9G′T	0.16	1.91	−1.75	1.71	**10**G′G	1.25	−4.95	6.20	1.48
9G′G	1.22	−5.58	6.80	1.43					
9G′G′	6.05	3.71	2.34	2.70					

All the values are in kcal/mol. Dipole moments (μ) are in debyes.

of 4-21G, and the pyramidality of the N is also underestimated.[18] The results in Table I show that all the basis sets including polarization functions predict the same energetic order. The addition of diffuse functions lowers the relative energy of the less stable conformers (maximum 0.4 kcal/mol), and the inclusion of the ZPE reinforces this lowering. The MP2 correction acts in the opposite direction, increasing the relative energy of the less stable conformers (maximum 1 kcal/mol), so that this effect is compensated by the former two. The MP2/6-31G**//MP2/6-31G** values also indicate that the effect of correlated geometrical optimizations on the relative energies is negligible. Furthermore, the results obtained for **1** at a higher computational level such as MP2/6-311+G(2d,p)//MP2/6-31G(2d,p)(9) (see Table I), agree with our HF/6-31G**//HF/6-31G** ones. According to the above, for the compounds studied and for the present purposes, the quality of the HF/6-31G** results can be considered sufficient, and therefore, this computational level was chosen as the reference for the follow-

ing discussion. For an extensive group of anomeric compounds, Salzner and Schleyer[11b] also considered that, except for fluorocyclohexane, HF/6-31G* results can be sufficient for the analysis of anomeric interactions. Even more, as some results become worse when MP2 correlation is considered, they suggested that correlation corrections with small Pople basis sets are artifacts due to basis set deficiencies. We have observed similar findings in the *ab initio* study of compounds with an endocyclic N—C—O unit,[11d] so that the mentioned compensation of effects seems to be independent of the cyclic or linear character of the anomeric N—C—O compounds.

The results of Table I show that, in several cases, GT is the most stable conformer, although it changes to TT in some compounds. Therefore, in opposition to that expected according to the anomeric effect, the preference for the R—O—C—N *gauche* orientation is not always observed. On the other hand, the more stable conformers always show *trans* Lp—N—C—O arrangements (that is, H—N—C—O in *gauche*), so that the anomeric effect in this case is clear. Due to the absence of anomeric stabilization, the most energetic conformer is always TG, accompanied by GG or G′G′ in the compounds in which these conformers have been located as minima, while GG′ and/or G′G are of intermediate stability. The methylation of the alcohol group (position R_1) invariably makes TT more stable than GT, increasing its stability about 1–1.5 kcal/mol, if compared with to the nonmethylated analogues (see the pairs **1**–**2**, **5**–**6**, **8**–**7**, **3**–**10**). For compounds without R_1-methylation, those structures displaying *gauche* H—O—C—N angles are preferred although other isoenergetic conformers accompany them (see **1**, **3**, **4**, **5**, **8**, and **9**). The mono- or bimethylation on C (positions R_4 and/or R_5) does not have any effect on the stability ordering. When one or two methyl groups are bonded to the N (positions R_2 and/or R_3), GT becomes more stable than TT, except when the oxygen is methylated, because this is a determining factor. With regard to the less stable conformers, it can be noted that methylation on R_2 or R_4 tends to reduce their relative energy about 0.6–1 kcal/mol, while no systematic behavior is shown for R_1-methylated compounds.

The geometrical parameters (see supplementary material) display the tendencies associated with the anomeric effect already described individually in other studies.[12, 13, 17–19] The following general observations should be noted: TT, GT, and G′T show larger C—O bond lengths, because these bonds are *trans* oriented to an N lone pair. For the same reason, the C—N bonds are shorter in TT, TG, and TG′, because they are not *trans* oriented to the O lone pair. The C—N shortening is smaller than the C—O lengthening, because, as will be shown below, according to the NBO method, the *anti* n_N–σ^*_{CO} interaction is stronger than the anti n_O–σ^*_{CN} one. Even more, the maximum C—N or C—O lengthening, due to a favorable anomeric orientation, corresponds with the maximum C—O or C—N shortening. The N—C—O angle is also opened due to the *trans* orientation of the C—O and/or C—N bonds and a lone pair, showing quasi-additive systematic variations. Thus, the GT and G′T conformers show larger N—C—O angles, as a result of two simultaneous *trans* orientations, while TT, GG′, and G′G, with only one *trans* orientation, have almost identical intermediate angles. Invariably, TG and TG′ display the smallest N—C—O values, because of the absence of the anomeric effect. The $R_{i\ (i=4,5)}$—C—X (X = O, N) angles also follow the expected pattern, widening notably when R_i is *trans* oriented to a lone pair of X. It should be pointed out that n_N–$\sigma^*_{C\text{-}Ri}$ interactions are also stronger than n_O–$\sigma^*_{C\text{-}Ri}$ interactions. The values of the R_1—O—C angle could be related with steric effects, being larger for $R_1 = CH_3$ compounds (**2**, **6**, **7**, and **10**) than for R_1 = H. The R_1—O—C widening is even increased in the more restrained conformers, GT and GG′. The variations of the $R_{i\ (i=2,3)}$—C—N angles are also associated with steric effects, so that they are systematically opened in the more restrained conformers.

AMINOMETHANOL (1)

The energy ordering **1**GT ≅ **1**TT < **1**GG′ ≪ **1**TG can be interpreted using the NBO method (Table II). Many NBO studies have shown that the effect of the charge delocalization should not be analyzed by only comparing lone pair–antibond interactions of the type n_X–σ^*_{CY}, n_X–σ^*_{XH}, and n_X–σ^*_{CH} between conformers, because other bond–antibond interactions such as σ_{CH}–σ^*_{XH}, σ_{XH}–σ^*_{CX}, etc., can have different relative importance.[11] However, in **1**, the analysis of these bond–antibond interactions shows that they are quite similar for all the conformers. According to this, the hyperconjugative preference for **1**GT over **1**TT (4.1 kcal/mol) is caused fundamentally by the difference between a n_O–σ^*_{CN} interaction in **1**GT, which is stronger than n_O–σ^*_{CH} in **1**TT. Even more, **1**GG′ is less stable than **1**GT, mainly because the n_N–σ^*_{CH} interaction in **1**GG′ is less intense than n_N–σ^*_{CO} in **1**GT, and the same can be observed if comparing **1**TG and **1**TT. Without considering hyperconjugation, the E_{Lew} column indicate a very

different energy ordering, that is, **1**GG′ < **1**TT ≅ **1**TG ≪ **1**GT. The large Lewis energy for **1**GT could be related to repulsions between aligned O—H and N—H bonds. Previous NBO studies have shown that repulsions between lone pairs are smaller than between bonds, although the nature of these repulsions cannot be determined by the NBO method.[11] According to this, the aligned interactions in **1**GT change to smaller n_O/n_N, n_O/NH, or n_N/OH ones in the other conformers. Thus, the energy ordering of the conformers favored by one or two anomeric interactions is mainly due to hyperconjugation, which is more important than E_{Lew}. From the analysis of the NBO results, it can be also seen that the *anti* n_N–σ^*_{CO} interaction is stronger than the *anti* n_O–σ^*_{CN} one, so that the N lone pair is a better donor than the O lone pair, and σ^*_{CO} is a better acceptor than σ^*_{CN}. An analogous conclusion was achieved by an analysis procedure different and independent of the NBO method,[9] and from the analysis of some 3-21G//3-21G results.[18] It should be remarked that the present explanation for the origin of the anomeric effect in **1** also agrees with that suggested by Smits et al., based on interference interactions,[1c] because hyperconjugation and interference interactions can be considered different representations of the same basic physical phenomenon.[11a]

The comparison between methanediol (HO—CH_2—OH, **11**), and aminomethanol (HO—CH_2—NH_2, **1**) allows us to analyze the repercussion that the substitution of O for N has on the anomeric effect. Salzner and Schleyer[11a] optimized the conformers of **11** at the MP2/6-31G** level, and then analyzed the HF/6-31G** wave functions with the NBO method. The less stable conformer, **11**C_{2v}, has relative E_{tot}, E_{del}, and E_{Lew} values of 8.3, 6.6, and 1.7 kcal/mol with respect to the most stable conformer, **11**C_2 (see Table III in ref. 11a). These conformers are equivalent to **1**TG′ and **1**GT, respectively, with E_{tot}, E_{del}, and E_{Lew} relative values of 5.0, 8.3, and −3.3 kcal/mol (see Table II). Therefore, when the O is changed to N the energy difference between comparable conformers reduces, although **1**TG′ is probably less favored by the anomeric effect than **11**C_{2v}. The NBO contributions show that substitution increases the hyperconjugative preference for **1**GT over **1**TG′ (compared to **11**C_{2v} over **11**C_2), although the effects contained in E_{Lew} favor notably **1**TG′. The E_{del} values are related to the different interactions present in both molecules, that is, n_O–σ^*_{CH} and n_O–σ^*_{CO} (in **11**C_{2v} and **11**C_2, respectively) change to n_N–σ^*_{CH} and n_N–σ^*_{CO}, or n_O–σ^*_{CN} (in **1**TG′ and **1**GT, respectively). According to these changes, the donor character is increased due to the presence of the N pair, and the acceptor character is reduced because of the presence of the σ^*_{CN} antibond, being the net effect the stabilization of the **1**GT conformer. The drastic change in the Lewis energy difference could be related to the increased parallel repulsions as a consequence of substitution. Thus, one oxygen lone pair and one O—H bond are aligned in **11**C_2, while the O—H and N—H bonds are aligned in **1**GT. It was stated above that repulsions between bonds are larger than repulsions between lone pairs and bonds; therefore, the Lewis energy of **1**GT increases and the **1**TG′ conformation is favored. Remarkably, the Lewis energy change caused by substitution (about 5 kcal/mol) is similar to the Lewis energy difference between **1**GG′ and **1**GT conformers (5.03 kcal/mol favoring **1**GG′), where parallel n_O/O—H repulsions in **1**GG′ also change to O—H/N—H in **1**GT.

We have also employed the NBO method to interpret the origin of the rotational barriers around the C—O and C—N bonds. Figures 2 and 3 represent the relative energies for a series of structures optimized with a fixed dihedral angle in a favorable anomeric orientation, that is (H—O—C—N; T) and (G; Lp—N—C—O), respectively. As can be seen in Figure 2, the barrier around the C—O bond is mainly due to a positive delocalization contribution, not compensated by the negative electrostatic and steric effects included E_{Lew}. The barrier for intercon-

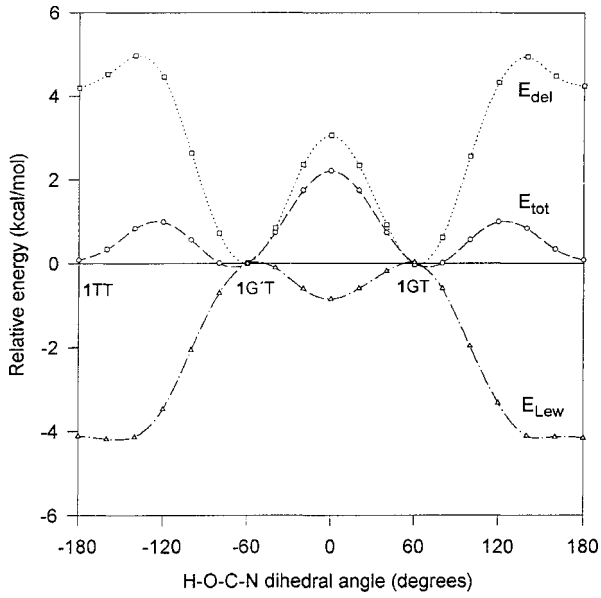


FIGURE 2. Rotational barrier (E_{tot}) around the O—C bond of aminomethanol (**1**). Delocalization (E_{del}) and Lewis energies (E_{Lew}) obtained aplying the NBO method on HF/6-31G** wave functions.

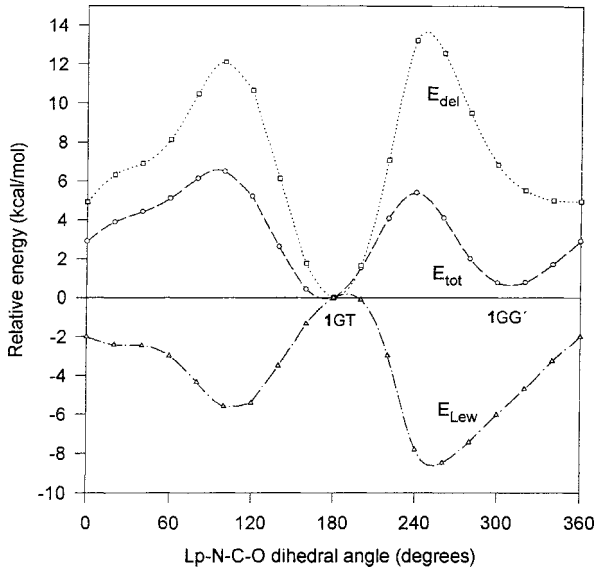


FIGURE 3. Rotational barrier (E_{tot}) around the N—C bond of aminomethanol (**1**). Delocalization (E_{del}) and Lewis energies (E_{Lew}) obtained aplying the NBO method on HF/6-31G** wave functions.

version between **1**GT and **1**G′T, located around 0°, owe their origin to E_{del} more than to E_{Lew}, while the interconversion between **1**TT and **1**GT, around 120°, has a lower energy cost because of the balance of effects. The rotational barrier around the C—N bond (Fig. 3) is also mainly due to hyperconjugation, because the variation of the potential energy is almost parallel to the delocalization term, which is always positive and larger in absolute value than the negative Lewis contribution. The value of the Lp—N—C—O dihedral angle for the **1**GT minimum is due to delocalization, while the structure of **1**GG′ (Lp—N—C—O = −50°) results from the compromise between the position of the minima of the Lewis (−110°) and delocalization (0°) contributions.

1-METHOXY-METHANAMINE (2)

From Table I it can be deduced that the methylation on the oxygen (R_1) does not alter the number of stable conformers, although the stability of the two more stable forms (**2**TT and **2**GT) is inverted if compared with the analogues of **1**. This preference for the *anti* orientation exhibited by the Me—O—C—N moiety in **2**TT corresponds to the so-called reverse anomeric effect.[1f, 1g] Altona et al.[17] reported reverse anomeric effects in X—CH_2—O—CH_3 (X = NH_2(t), NH_3^+) in agreement with the experimental evidence.[1f] Following the arguments of Praly and Lemieux,[1f] and Booth,[1g] they conclude that a competition exists between various anomeric interactions present in the molecules, but it remains unclear if the reverse anomeric effect is a result of electronic or steric interactions or both. The NBO method may help to clarify this question. Thus, the delocalization term is almost unchanged when passing from **1** to **2**, although an O—H bond is replaced by an O—C one. The energy differences between the important hyperconjugative interactions are the same in **1** and **2**, and hence, E_{del} again favors **2**GT by 4.6 kcal/mol. However the energy difference ΔE_{Lew}(**2**TT–**2**GT) is −5.5 kcal/mol compared with −4.0 kcal/mol for **1**, so that the inversion of the total relative energy seems to be caused by the increase of the repulsions in **2**GT due to the R_1 methyl group in *gauche* orientation. Two additional features reinforce this idea and point to steric effects as responsible for the reverse anomeric effect in **2**. On the one hand, the shortest nonbonded distance $H_{(CH3)}\cdots H_N$ is 4.12 Å in **2**TT and 2.42 Å in **2**GT, and the R_1—O—C—N angle (see supplementary material) in **2**GT is far from its ideal value (72.5°). On the other hand, the total dipolar moments of the TT and GT conformers of **1** and **2** are similar, and the dipolar interactions are probably comparable (only the O—H dipole in **1** change to O—C in **2**). These features suggest that the electrostatic effects included in E_{Lew} would not change appreciably with the methylation. According to the above, the expected higher hyperconjugative preference for **2**GT would be reduced by steric impediments, and the inverted stabilities of **2**TT and **2**GT conformers (compared to **1**TT and **1**GT) seems not to be related with the electronic competition suggested in the literature.

The comparison between the (C—O—C—N; T) (Fig. 4) energy curve and its analogue for **1** (Fig. 2) indicates that the rotational barrier around the O—C bond has the same origin as that already described for **1**. The only difference is the higher energy cost for the **2**GT ↔ **2**G′T interconversion around 0°, because of the positive Lewis energies caused by the interactions between the OCH_3 and NH groups in this rotational region. The delocalization term, which has essentially not undergone a change in behavior, adds up to the E_{Lew} term. On the other hand, the barrier around the N—C bond for **2** remains unaltered if compared with **1** (see Figs. 3 and 5), with similar behavior of both Lewis and delocalization contributions, so that the methylation on the oxygen has no repercussions in this respect.

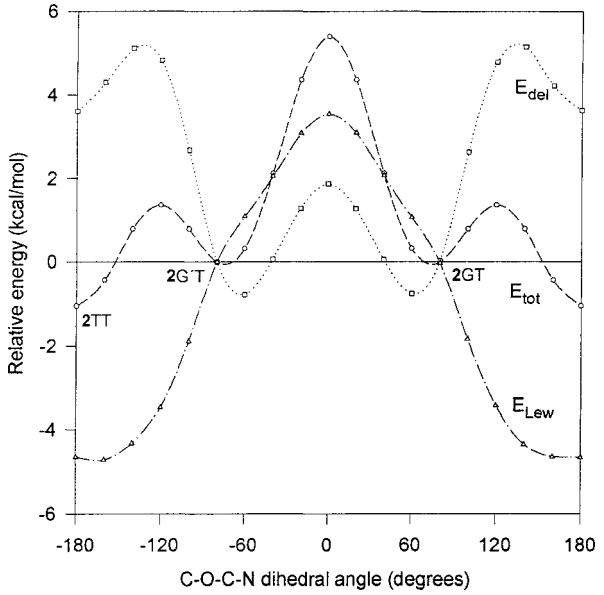


FIGURE 4. Rotational barrier (E_{tot}) around the O—C bond of 1-methoxy-methanamine (**2**). Delocalization (E_{del}) and Lewis energies (E_{Lew}) obtained aplying the NBO method on HF/6-31G** wave functions.

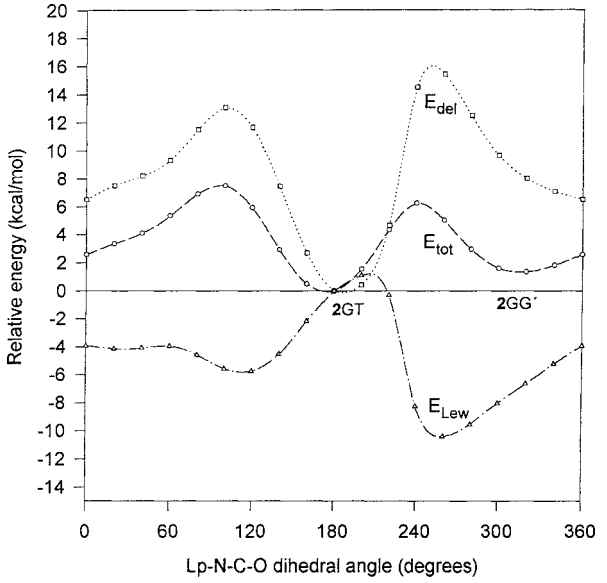


FIGURE 5. Rotational barrier (E_{tot}) around the N—C bond of 1-methoxy-methanamine (**2**). Delocalization (E_{del}) and Lewis energies (E_{Lew}) obtained aplying the NBO method on HF/6-31G** wave functions.

OTHER METHYLATED DERIVATIVES

1-Aminoethanol (3)

Although the asymmetry resulting from the methylation on the carbon causes a slight energetic breakdown of the enantiomers of **1**, the NBO contributions (Table II) indicates that the origin of the energy ordering is the same for **3** and **1**. The only notable effect is that **3**GG′ and **3**G′G become more stable due to the higher compensation of E_{del} with E_{Lew}. The energy differences ΔE_{del}(**3**TG′–**3**TG), ΔE_{del}(**3**G′T–**3**GT), and ΔE_{del}(**3**GG′–**3**G′G) are positive because in each pair there is one n_X–σ^*_{CH} interaction that changes to a less stabilizing n_X–σ^*_{CC} one (X = N or O). The dipole moments of the members of each pair are almost identical, so the Lewis energy differences could be attributed to the steric effects produced by the R_5 methyl group.

2-Amino-2-propanol (4)

As can be seen in Table II, if compared with **1**, the double methylation on the carbon does not alter appreciably the relative energies of the conformers of **4**, which indicates the same origin for the conformational preferences. The importance of hyperconjugation in **4** is smaller than in **1** because those orbital interactions, including the σ^*_{CH} antibond, have changed to σ^*_{CC}. In the same way, the absolute values of E_{Lew} are smaller than in **1**, in accordance with the smaller dipolar interactions expected when the CH dipole is replaced by the CC dipole. The decrease of the Lewis relative energies could be also related to the smaller dipolar moment of the conformers of **4**, compared to those of **1**. From the comparison between **1**, **3**, and **4**, it can be seen that methylation on the C reduces, in an additive way, the relative energy of the less stable conformers.

Methylaminomethanol (5)

When a methyl group is bonded to the nitrogen, the delocalization and Lewis energies of **5** are comparable to those of **1**, given that they are caused by the same important orbital interactions and by the same repulsions, respectively. The delocalization energy differences between the members of the pairs **5**TG/**5**TG′, **5**G′G/**5**GG′, and **5**GG/**5**G′G′ are due to different bond–antibond interactions for the *anti* or *gauche* orientations of the R_3 methyl group with respect to the C—O bond. The methyl group orientation also justifies the E_{Lew} differences in each pair, caused by steric impediments. It should be noted the GG and G′G′ forms were characterized as energy minima in **5**, as in **6**, **8**, and **9**. A common feature of these compounds is the presence of a methyl group on the N, while in its absence the GG and G′G′ conformations have always been

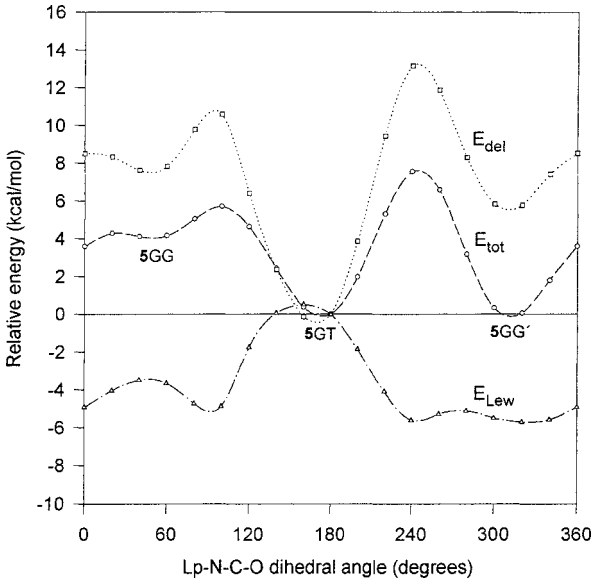


FIGURE 6. Rotational barrier (E_{tot}) around the N—C bond of methylaminomethanol (**5**). Delocalization (E_{del}) and Lewis energies (E_{Lew}) obtained aplying the NBO method on HF/6-31G** wave functions.

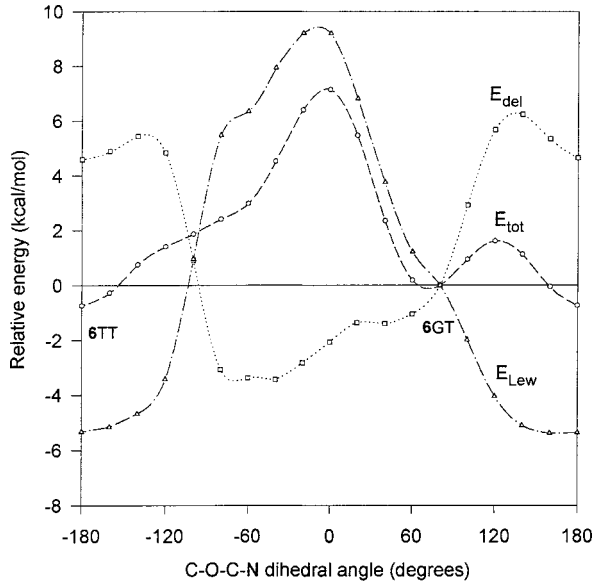


FIGURE 7. Rotational barrier (E_{tot}) around the O—C bond of 1-methoxy-*N*-methylmethanamine (**6**). Delocalization (E_{del}) and Lewis energies (E_{Lew}) obtained aplying the NBO method on HF/6-31G** wave functions.

characterized as transition states. Hence, according to Figure 6, the local **5**GG minimum is due to a minimum of the delocalization term, caused by the methyl group, which does not exist in compounds such as **1** (Fig. 3) or **2** (Fig. 5). It is also important to note that *N*-methylation increases the stability of the high energy conformers **5**TG and **5**GG′.

1-Methoxy-*N*-methylmethanamine (6)

As occurred in **2**, due to the presence of a R_1 methyl group, **6**TT is more stable than **6**GT. The E_{tot}, E_{del}, and E_{Lew} values are similar for both molecules, which suggest the existence of the same effects, that is, the steric impediment in **6**GT is opposed to the stabilizing anomeric effect. As occurred in **5**, due to the asymmetrical R_2 methylation, the E_{del} and E_{Lew} differences for the pairs **6**TG/**6**TG′ and **6**GG′/**6**G′G can be adequately explained by the *anti* or *gauche* orientation of the methyl group. According to the energy curve shown in Figure 7, the absence of the **6**G′T conformer (with C—O—C—N angle around −60°), although favored by hyperconjugation, is due to the high Lewis energy in that rotational region. The reason for this E_{Lew} increase could be related with the steric interaction between the parallel R_1 and R_2 methyl groups located on the same side of the plane formed by the N—C—O atoms.

1-Methoxy-*N*, *N*-dimethylmethanamine (7)

Due to the presence of three R_1, R_2, and R_3 methyl groups, several conformational aspects arise. First, the extra stability of **7**TT, as was noted above, is due to the R_1 substitution. Second, the **7**GT form was not characterized as an energy minimum, clearly due to steric impediments. As can be seen in Figure 8, the flat energy curve for the delocalization term between −60° and +60° would favors the **7**G′T and **7**GT forms, but the Lewis energy is very unfavorable, and is also responsible for the rotational barrier. As before, a high degree of methylation reduces the relative energy range and the dipolar moment, as observed if comparing the values for the TG conformers of the compounds **1**, **2**, **6**, and **7**.

Dimethylaminomethanol (8)

The conformational preferences in **8** are similar to those of **1**, but the **8**GG conformation is now stable. As was suggested in **5**, *N*-methylation is the responsible for the appearance of the new conformer. When the number of methyl-groups bonded to the N increases, there is also a cumulative reduction of the relative energy of the less stable conformers, as can be seen by comparing the E_{tot} values for TG, GG, and GG′ in the series **1**, **5**, and **8**. As a consequences of this effect, **8**GG′ becomes more stable than **8**GT.

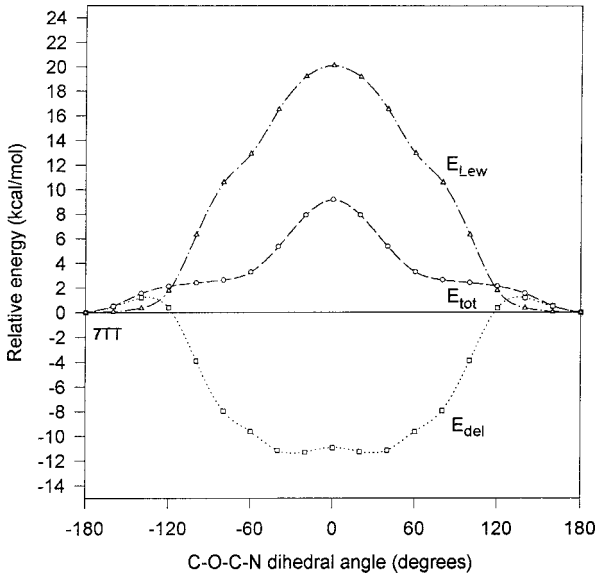


FIGURE 8. Rotational barrier (E_{tot}) around the O—C bond of 1-methoxy-*N*,*N*-methylmethanamine (**7**). Delocalization (E_{del}) and Lewis energies (E_{Lew}) obtained aplying the NBO method on HF/6-31G** wave functions.

1-Methylaminoethanol (9)

The same conformational features already described for **3** and **5** can be observed in **9**. It should be noted, however, the high instability of **9**TG′ and **9**G′G′ is caused by their Lewis energies. These increased values could be due to the steric interactions between the R_3 and R_4 methyl groups, because the dipolar moments for comparable conformers of **3**, **5**, and **9** do not change appreciably.

1-Methoxy-1-aminoethanol (10)

The same effects described in **2** and **3** are present in **10**. Thus, due to the R_1 methylation, the **10**GT conformer is the most favored by delocalization, but steric effects destabilize it. This compound is the only methylated on R_1, where TT is not the most stable conformer, although the nonbonded interactions between the R_1 and R_5 methyl groups do not increase E_{Lew} for **10**TT, if compared with the values for **3**. It should be noted (see supplementary material) that **10**TT present the more deviated R_1—O—C—N angle (−159.83°), with respect to the 180° ideal value, of all the compounds studied, so that, the n_O–σ^*_{CH} and n_N–σ^*_{CO} interactions are produced far from the *anti* orientation, and the charge delocalization in **10**TT is reduced. The same explanation underlies in the high E_{del} values of **10**TG, which has a very distorted R_1—O—C—N angle (−142°) to reduce the steric impediment between methyl groups.

INFLUENCE OF THE SOLVENT

To the authors' knowledge, the conformational preferences in water for the compounds presented here were not analyzed previously, and only Tomasi et al.[20] studied the influence of the basis set on the aqueous conformational energies for three restrained conformations of **1** employing STO-3G, 3-21G, and 4-21G calculations. Therefore, the HF/6-31G** relative energies in aqueous solution (E_{wat}) for the stable conformers previously located in the gas phase are shown in Table III. The electrostatic (ΔG_{el}) and nonelectrostatic components (ΔG_{noel}) of the free solvation energies (ΔG_{sol}) are also included. If these values are compared with those previously shown in Tables I or II, it can be observed that the presence of water appreciably modifies the relative stabilities, and even for **4**, **5**, and **9**, the most stable conformer is different in solution and in the gas phase. For all the compounds, the most significant variations in relative energies are produced in the TG, TG′, GG, and G′G′ conformers, which turn out to be stabilized between 1 and 3 kcal/mol.

Although numerous cases have been reported on attenuation of the anomeric effect due to the presence of a polar solvent,[14] in the series of compounds studied here, this feature is not clearly appreciable. Hence, contrary to expectations, for the GT/G′T and TT conformers where the presence of anomeric interactions was clearly established in the gas phase, the relative energies in solution and in the gas phase are not remarkably different. Moreover, in some cases (e.g., **1**GT) the conformer with larger anomeric interactions is even slightly stabilized by the solvent.

The analysis of the free solvation energy components allows us to explain these tendencies. As can be seen from Table III, the electrostatic term is the main responsible of the variations in relative energies, because the nonelectrostatic component is practically constant for the conformers of each compound. In accordance with this, the conformers more stabilized by the solvent (TG, TG′, GG, and G′G′) present higher ΔG_{el} values and larger dipolar moments. However, a direct relationship between the value of the total dipolar moment and ΔG_{el} cannot be observed; hence, local electrostatic interactions between the different groups of the molecule and the solvent may be important.[11d, 20] Those conformers with high dipole moment present the lone pairs of O and N situated on the same

TABLE III.

HF/6-31G Relative Energies in Water (E_{wat}) Calculated with the PCM Method (See Text for Computational Details).**

	E_{wat}	ΔG_{sol}	ΔG_{el}	ΔG_{noel}		E_{wat}	ΔG_{sol}	ΔG_{el}	ΔG_{noel}
1TT	0.55	−7.93	−10.13	2.20	**2**TT	0.00	−3.80	−7.26	3.46
1TG	3.29	−10.00	−12.14	2.14	**2**TG	2.89	−5.79	−9.19	3.40
1GT	0.00	−8.32	−10.55	2.23	**2**GT	0.57	−4.06	−7.58	3.52
1GG′	1.39	−7.53	−9.66	2.13	**2**GG′	2.29	−3.93	−7.36	3.43
3TT	0.79	−5.71	−9.36	3.65	**4**TT	0.00	−3.46	−8.81	5.35
3TG	3.38	−7.89	−11.52	3.63	**4**TG	2.63	−5.04	−10.34	5.30
3TG′	3.02	−7.38	−10.99	3.61	**4**GT	−0.37	−3.90	−9.22	5.32
3GT	0.38	−6.19	−9.88	3.69	**4**GG′	0.21	−3.32	−8.58	5.26
3GG′	1.12	−5.53	−9.12	3.59					
3G′T	0.00	−6.46	−10.10	3.64					
3G′G	1.19	−5.40	−9.00	3.60					
5TT	0.38	−4.90	−8.46	3.56	**6**TT	0.00	−0.79	−5.72	4.93
5TG	2.45	−6.63	−10.08	3.45	**6**TG	1.77	−2.92	−7.75	4.83
5TG′	2.19	−6.82	−10.34	3.52	**6**TG′	2.43	−2.32	−7.07	4.75
5GT	0.00	−4.85	−8.48	3.63	**6**GT	0.48	−0.92	−6.03	5.11
5GG	1.55	−7.63	−11.14	3.51	**6**GG′	2.08	−0.49	−5.67	5.18
5GG′	0.36	−4.59	−8.15	3.56	**6**G′G	1.67	−0.63	−5.66	5.03
5G′T	−0.64	−5.51	−9.14	3.63	**6**G′G′	3.23	−2.60	−7.47	4.87
5G′G	0.66	−4.44	−7.94	3.50					
5G′G′	2.14	−6.75	−10.33	3.58					
7TT	0.00	2.43	−4.10	6.53	**8**TT	0.58	−1.96	−7.03	5.07
7TG	1.57	0.81	−5.46	6.27	**8**TG	1.80	−3.64	−8.47	4.83
7GG′	0.90	2.49	−3.98	6.47	**8**GT	0.33	−1.48	−7.03	5.55
					8GG	1.61	−3.63	−8.56	4.93
					8GG′	0.00	−1.56	−6.44	4.88
9TT	0.46	−2.78	−7.86	5.08	**10**TT	0.54	−1.99	−6.92	4.93
9TG	3.30	−3.85	−8.87	5.02	**10**TG	3.93	−3.40	−8.41	5.01
9TG′	4.24	−4.62	−9.74	5.12	**10**TG′	2.81	−3.56	−8.52	4.96
9GT	0.00	−2.95	−8.03	5.08	**10**GT	2.17	−2.02	−7.19	5.17
9GG	2.33	−5.19	−10.22	5.03	**10**GG′	3.59	−1.62	−6.69	5.07
9GG′	1.90	−2.41	−7.61	5.20	**10**G′T	0.00	−1.95	−7.00	5.05
9G′T	−0.16	−3.27	−8.44	5.17	**10**G′G	1.40	−1.79	−6.77	4.98
9G′G	1.73	−2.44	−7.58	5.14					
9G′G′	4.30	−4.70	−9.93	5.23					

Solvation energies (ΔG_{sol}) and its electrostatic (ΔG_{el}) and nonelectrostatic (ΔG_{noel}) contributions are also shown. All the values are in kcal/mol.

side of the molecule, and opposed to the O—R and N—R bonds (see Fig. 1). The solvent especially stabilizes these structures because two regions of very different polarity are located in separated regions of the molecule.[20] Moreover, in most cases, the GG′/G′G conformers are less stabilized by the solvent than GT/G′T or TT, despite having higher total dipole moments. Because in GG′/G′G the O and N lone pairs are parallel to the N—H and O—H bonds, respectively, there are regions of different polarity that get close together, and the electrostatic solute–solvent interaction is reduced. Finally, the GT/G′T and TT conformers are intermediate situations between the previous two (GT/G′T have O—R and N—R bonds on the same side of the molecule, and TT has the O lone pairs and the N bonds in separated spatial regions) whence, despite showing anomeric effect, they do not become destabilized in aqueous solution.

The values of the electrostatic contribution confirm the importance of the local dipolar interactions between solute and solvent. Thus, when a

methyl group is introduced the value of ΔG_{el} is smaller, approximately 2.5–3.0 kcal/mol for O—Me, 1.5–2.0 kcal/mol for N—Me, and 0.7 kcal/mol for C—Me. The effect is additive when more than one methylation occurs. This tendency can be related to the local change in polarity due to the substitution of a X—H bond for a less polar one such as X—Me, which would cause a reduction of the stabilizing solute–solvent interaction. Moreover, the reductions mentioned coincide with the increasing polarity of the bonds, which are substituted, that is $\mu_{O—H} > \mu_{N—H} > \mu_{C—H}$. On the other hand, we should also highlight the additivity of the nonelectrostatic term, which increases approximately by 1.5 kcal/mol for each methyl group introduced, although in this case independently of the position of methylation.

Conclusions

The relative conformational stability of aminomethanol and methylated derivatives can be properly described at the HF/6-31G**//HF/6-31G** level. These results are almost unchanged if other effects are considered (augmenting the basis set, electron correlation, and ZPE), because they tend to compensate each other. The relative energies agree with the known tendencies expected for the generalized anomeric effect, that is, the more stable conformers display two *trans* orientations between an O or N lone pair and a polar C—N or C—O bond. The *trans* Lp—N—C—O arrangement has been found to be clearly more favorable than the Lp—O—C—N one. However, the presence of a methyl group bonded to the oxygen has a remarkable influence on this conformational preference, because the *gauche* Lp—O—C—N orientation (that is, *anti* R—O—C—N) always becomes the most stable one. This trend is independent of the rest of substituents on the carbon and/or the nitrogen. The methylation on the carbon does not alter the energy ordering, while the methylation on the nitrogen slightly reinforces it. Both methylations cause a quasi-additive increase in the stability of the less favored conformers. Some geometrical trends agree systematically with those expected for systems with anomeric interactions. These trends are slightly altered in some cases by steric effects, which also behave in a systematic way.

According to the NBO analysis, the conformational preference for the mentioned *trans* orientations (generalized anomeric effect) in aminomethanol is mainly due to charge delocalization. The stabilization produced by delocalization is always higher than the energy of the conformers considered as hypothetical Lewis structures, so that the electrostatic and steric contributions are less important. These conclusions based on NBO calculations are in agreement with those reached by other independent procedures based on different energy decomposition models. The comparison between the NBO results for methanediol and aminomethanol indicates that, although the energy ordering remains unchanged, the substitution of an O for an N (passing from the O—C—O unit to the N—C—O) reduces the stability of the favored conformers. This reduction is due to an unfavorable repulsion between aligned O—H and N—H bonds, which exceed the hyperconjugative stabilization caused by the substitution. The influence of methylation in the different molecular positions on the relative stability can be explained systematically by analyzing the alterations on the n_X–σ^*_{CY} interactions, and by the associated steric effects produced by the presence of the methyl groups. Thus, the reverse anomeric effect observed for those O-methylated compounds is probably due to the steric effects. With regard to the rotational barriers of aminomethanol around the C—O and C—N bonds, the NBO analysis suggests that they are due fundamentally to hyperconjugation, always positive, and not compensated with the electrostatic and steric effects, always negative. A coherent explanation was found for the influence of the methylation on these rotation barriers. Although they are always mainly caused by charge delocalization, due to methylation, steric effects can also become important, as was observed for rotations around the C—O bond.

The influence of water on the relative stabilities of the conformers studied was determined. The electrostatic component of the solvation energy is mainly responsible for the energetic variations observed, and depends to a great extent on the local solute–solvent dipolar interactions. These local interactions also stabilize those conformers displaying anomeric interactions, and for this reason, in contrast with previous studies of other anomeric systems, for aminomethanol and methylated derivatives the presence of a polar solvent does not significantly reduce the preference for conformers showing an anomeric effect. The most remarkable influence caused by the solvent is the reduction of the relative energies of the more unstable conformers (between 1 and 3 kcal/mol). This energetic reduction is related with the existence of regions of different polarity (lone pairs and bonds) on opposite sides of the molecule, a structure strongly stabilized by the solvent.

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